Links between persistent DNA damage, genome instability, and aging

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There is considerable overlap between cellular and molecular changes that occur in response to low doses of ionizing radiation and those that occur during aging. Both processes are characterized by accumulation of persistent DNA damage ("wear and tear" on the genome), accumulation of protein and lipid oxidation products, loss of regenerative capacity at the cellular and tissue level, and increased incidence of cancer. These observations support a hypothesis that exposure to low-dose ionizing radiation accelerates normal, aging-related tissue changes.

We have investigated this hypothesis using a genetically tractable model organism, the Japanese medaka fish. The medaka is a whole-animal vertebrate model that preserves some of the advantages of cell culture systems, including low cost, fast results, ease of gene activation and silencing, and accessibility to optical microscopy.

To identify quantifiable endpoints of normal aging, a population of medaka fish was maintained under laboratory conditions until mortality was >90%. The median lifespan under these conditions was 22 months. Selected individuals were subjected to detailed histologic analysis at 6, 16, and 24 months of age. Analysis of sections containing dermis and skeletal muscle showed age-associated decline in dividing cells in the proliferative basal layer of the dermis and concomitant increase in senescence-associated β-galactosidase. The eye showed loss of pigmented cells in the retinal epithelium, and the heart showed age-associated appearance of lipofuscin and fibrotic tissue. The liver showed extensive age-associated changes, including spongiosis, accumulation of lipofuscin, a rise in the proportion of apoptotic cells and elevated levels of oxidized proteins. The lens of the eye, skeletal muscle and brain did not show evidence of age-associated changes. The results provide a set of quantifiable endpoints that can be used to investigate genetic and environmental influences on aging.

To investigate effects of radiation exposure on aging, we exposed medaka to a single acute dose of gamma radiation early in embryonic life. Consistent with findings reported by Egami and coworkers nearly 40 years ago (Egami and Eto, *Exp Gerontol* 8:219-222 (1973)), we found that a single sublethal exposure in early life significantly increased mortality measured over a two-year span. We collected tissues from the irradiated populations. Preliminary results suggest extensive histopathological changes in liver of individuals with a history of radiation exposure during early life.

To address the potential influence of radiation-induced genome instability on aging, we plan similar analyses using genetically modified medaka strains bearing fluorescent reporter transgenes that are designed to indicate the presence of genome instability.

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